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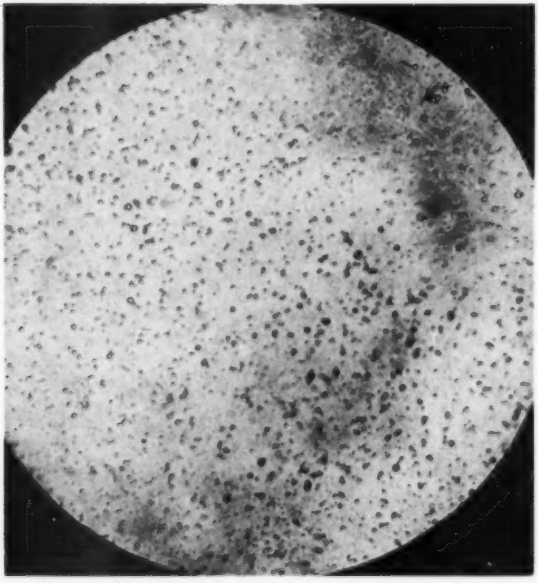

MICROPHOTOGRAPH OF AN AEROSOL
(see article on factors determining particle size)

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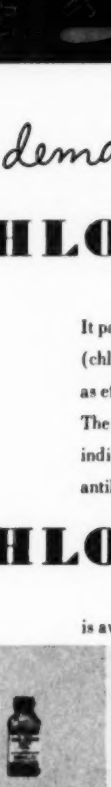

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Vol. 124 APRIL 1952 No. 4

CONTENTS

EDITORIAL

TUBERCULOSTATIC DRUGS

THE tremendous interest which has been aroused by the isonicotinic acid derivatives for the treatment of tuberculosis is readily understandable. Tuberculosis has been one of mankind's worst plagues, and volumes could be written on its impact on civilized man. Even today, tuberculosis exacts a terrible toll of human life and suffering; in some areas of the world it is the greatest health hazard.

While the early reports on the isonicotinic acid derivatives look very promising it would be well for us to adopt a conservative attitude regarding this latest "wonder drug." Other drugs and treatments have built up our expectations concerning the conquest of tuberculosis only for us to learn after extensive trial that they had very definite limitations. This has been the case with streptomycin, para-aminosalicylic acid, Tibione and BCG vaccine. All of these, of course, are useful drugs and they have greatly reduced both the morbidity and mortality caused by tuberculosis.

The great difficulty with tuberculostatic drugs in the past has been their lack of rapid effect. The administration of streptomycin, for example, is necessary over long periods of time in tubercular infections. This permits the development of mutants which are streptomycin resistant. In time, since all of the susceptible organisms have been restrained or killed only the drug fast organisms remain, the patient is uncured and the drug useless. Of course, combined therapy such as with streptomycin and PAS still further reduces the development of drug resistance, since with two drugs mutants must be resistant to both, but resistance still develops. Tuberculosis is a disease wherein it is difficult to get at the organism, at least with most drugs. It is this which makes prolonged therapy necessary and drug fastness a great risk.

The speed with which penicillin works in most infections caused by penicillin sensitive organisms is a great advantage since there is less opportunity for mutant, resistant strains to develop. The speed with which the isonicotinic acid derivatives are claimed to act may therefore be a point of great superiority over other tuberculostatic

agents. The rapid subjective improvement produced in the patient is another great advantage as well as the relatively low cost. Both of these make the patient anxious for such therapy.

We must, however, again sound a word of caution against over-optimism, for only too often has disappointment been our lot. The sulfonamides in 1936 would cure over 90 per cent of all cases of gonorrhea; today they are effective in only about 30 per cent of cases. Staphylococci, resistant to penicillin, are becoming more and more common, and monilia infections often cause trouble, today, by reason of the extensive use of broad spectrum antibiotics. It seems that for every gain that we make in therapeutics we must accept some loss. That our gains exceed our losses is evident from vital statistics but no drug is without its potential hazard and limitations. Even the "miracle drugs", ACTH and cortisone, are not without their dangers and these are now being used more judiciously than in the beginning.

Nature is an exceedingly complex mechanism and he who by any device, drug or otherwise, begins to tamper with it often finds complications which could never have been predicted in advance. Agriculture, for example, in spite of insecticides has increased our insect population, sanitation has increased the incidence of poliomyelitis, a rich diet the incidence of degenerative diseases and insulin the incidence of diabetes.

Let us hope that the limitations imposed by the use of the isonicotinic acid derivatives in tuberculosis will be minimal and that this disease will be drastically curtailed here and abroad. To expect this without now unforeseen sequelae would be purely wishful thinking and not in accordance with the history of the past.

L. F. Tice

PARTICLE SIZE IN NEBULIZED AEROSOLS

By Frederic Palmer, Ph. D.* and Stuart S. Kingsbury, M. S.**

FOR nearly a century the efficacy of inhalation therapy for diseases of the respiratory tract has been recognized. General use of this technique has, however, awaited the development of apparatus for producing a satisfactory cloud, or mist. The atomized cloud to be inhaled should consist of droplets of uniform diameter in the range 1-2μ. Large droplets should be eliminated since they are inefficient and harmful (1,2). The degree to which this has been accomplished in the mist of very small droplets, or aerosol, produced by a commercial nebulizer is one of the topics discussed below. Others are the nature of the aerosol, the mechanism of its production, and its microphotography.

The methods of measurement of particle size in an aerosol fall into four groups:—(a) those that depend upon measurement of the speed of fall of individual droplets; (b) those that depend upon the scattering of light by a cloud of homogeneous particles; (c) electrical methods; (d) electron microscopy. These methods have been described recently by F. T. Gucker (3), hence with one exception will not be discussed further here. The method best adapted to the measurement of particle size in a mist of non-uniform liquid droplets in the requisite size range is the speed-of-fall method based on the validity of Stokes' Law. The radius of a droplet is

$$r = \frac{9\eta v^{1/2}}{2\varrho g} \qquad (1)$$

where v is the velocity of free fall of a drop of density ϱ through a uniform medium of negligible density whose coefficient of viscosity is η. The acceleration due to gravity is g. However, when the size of the droplet is comparable with the mean free path of the air molecules through which it falls, a correction factor must be applied. For droplets of diameter, calculated from equation (1), of 20μ this

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** Research Engineer, Franklin Institute, now Materials Engineer, Aircraft Armament Laboratory Johnsville, Pa.

AUTHOR'S NOTE: All microphotographs taken at 100X and reduced as shown.

factor reduces the diameter by about 0.3 per cent; for those of diameter 2μ by about 4 per cent; and for those of diameter $.2\mu$ by about 26 per cent. The speed-of-fall method is applicable to droplets whose diameters lie in the range 1.0-15μ.

Droplets of machine oil (sp. gr. = .90) sprayed from an atomizer were allowed to fall through a small hole in a brass plate and were timed with a stop-watch as they traversed a measured distance between cross-hairs in a miscroscope. By use of equation (1) it was found that the uncorrected droplet diameter ranged from 1.5μ to 14μ. However, the presence was noted of droplets with diameters some above and some below this range, though their speed of fall could not be measured with accuracy.

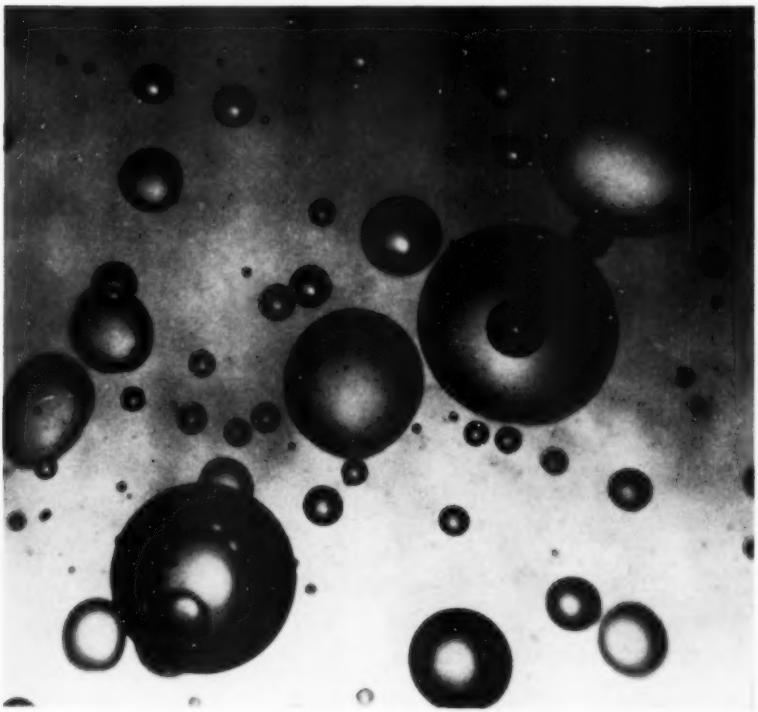


Fig. 1. Water Spray from DeVilbiss Atomizer on Glass Plate
Magnification 45X

Oily surfaces from previous use produced maximum vapor pressure in the measuring chamber, hence there was no evaporation from droplets of oil during observation. However, this was not true for other liquids. Nebulized droplets of diethylene glycol evaporated in 30 sec, and nebulized droplets of water in 3 sec.

If it is required to know not merely the range of particle size in an aerosol but also the size distribution in that range, the speed-of-fall method of measurement must be abandoned in favor of one in which the number of droplets in each of several ranges can be counted. The simplest way of doing this is by obtaining a permanent record by microphotography of a sampling of the aerosol collected upon a glass slide. The sampling method, however, is open to the following objections:—(a) evaporation may cause droplet diameter to change and the smallest droplets to disappear entirely before being photographed; (b) surface tension may cause the liquid to creep on the slide so that the droplets are no longer spherical; (c) two or more droplets may coalesce to form a single drop of large size; (d) some droplets may fall upon others and distort their outline; (e) droplets may be enlarged by (i) their own weight (especially the large ones), or (ii) the presence of diffraction rings in the microphotograph. These features are illustrated in Figure 1 which represents water spray from a hand-operated DeVilbiss atomizer collected

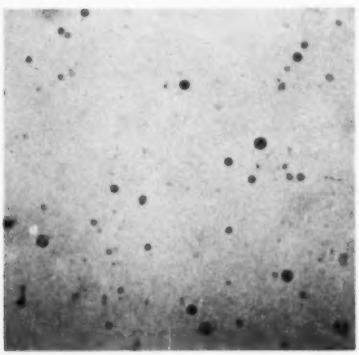


Fig. 2. Diethylene Glycol Mist from Vaponefrin Nebulizer. Mag. 75X

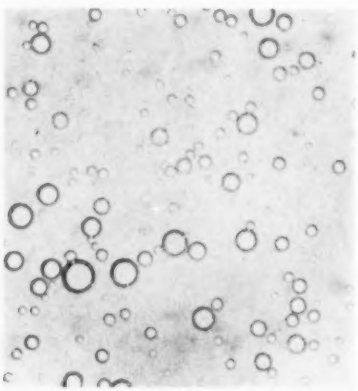


Fig. 10. Characteristic Spray from a "Flit" Gun Magnification 70X

on a glass plate at a magnification of 45X. It is evident that such an atomizer is not capable of forming a cloud of small droplets that are of nearly the same size. However, it has been pointed out (*2*) that nebulizers are now available that produce a reasonably uniform mist of droplets small enough to be useful as a therapeutic agent. Figure 2 shows a sampling of such a mist of diethylene glycol collected upon a clean microscope slide and photographed quickly so as to avoid evaporation. It appears that the desired conditions of size and uniformity are approached in such a nebulized aerosol and that an improvement in technique might make it possible to obtain by

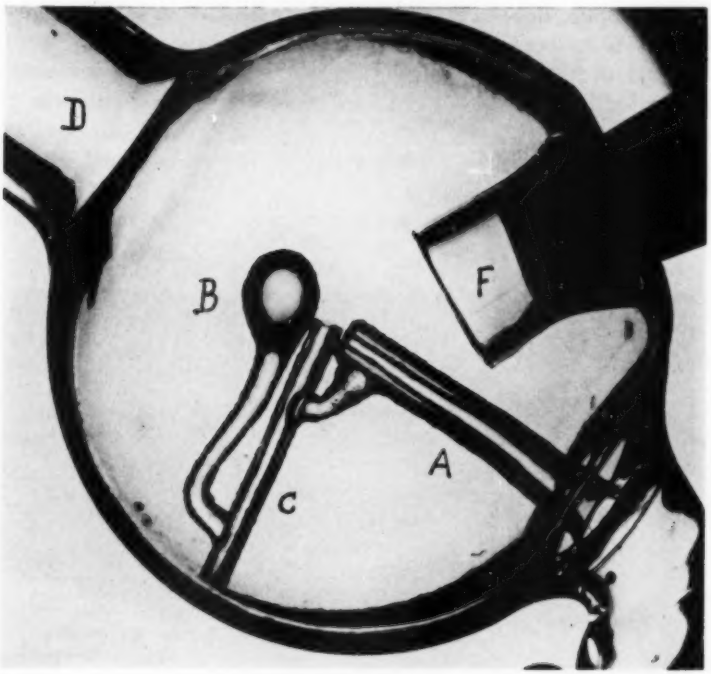


Fig. 3. Vaponefrin Nebulizer Showing Baffle and Position of Capillary and Air-jet

A. Air-jet
B. Baffle
C. Capillary
D. Delivery Tube
F. Filling Tube, Stoppered

mere inspection of the microphotograph all necessary information about the physical properties of the aerosol. To this end a study has been made of (a) the mechanism of nebulization, (b) the significant properties of the nebulized liquid, (c) the microphotographic technique.

It is well known that in the simple case of a cylindrical stream of falling water the shape remains stable until the length of the cylinder equals its circumference. Instability then sets in and the stream breaks up into drops which are alternately large and small (Plateau's spherule). Although the formation of droplets that are blown from the end of a capillary tube, as in a nebulizer, is doubtless more complex than this, it is difficult to see how it can help giving rise to both large and small drops. Hence the problem for the designer of a satisfactory nebulizer is that of providing a means of sifting the large drops out of the cloud before it issues from the exit tube.

In the Vaponefrin nebulizer this is accomplished by directing the atomized spray against a spherical baffle, as shown in Figure 3. The small droplets remain in the air which sweeps rapidly around

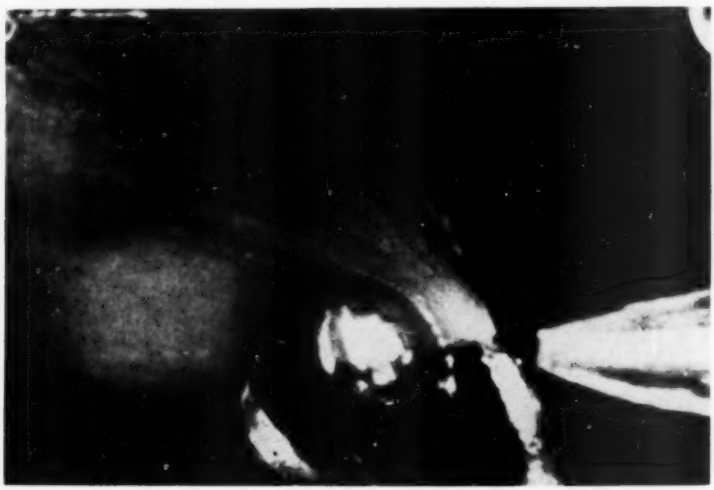


Fig. 4. Streams of Larger Drops Eliminated by the Baffle from the Cloud of Small Ones Seen Unresolved as a White Patch to the Left (By Permission)

the baffle and moves more slowly toward the exit; but the large droplets are eliminated in one or all of three ways:—they may crash into the baffle and break up into smaller droplets; they may break and unite with the layer of liquid that already covers the baffle; they may bounce off the baffle and cut across the paths of the smaller particles ultimately terminating upon the walls of the vessel. In Figure 4 they have been caught in the act. The streams of droplets seen are composed of the larger ones that will terminate on the walls of the vessel. The magnification (only 5X) is too low to resolve the smaller droplets in the cloud that appears as a white patch to the left of the baffle. In taking these photographs a 1/20,000 second electronic flash stroboscope was used for illumination.

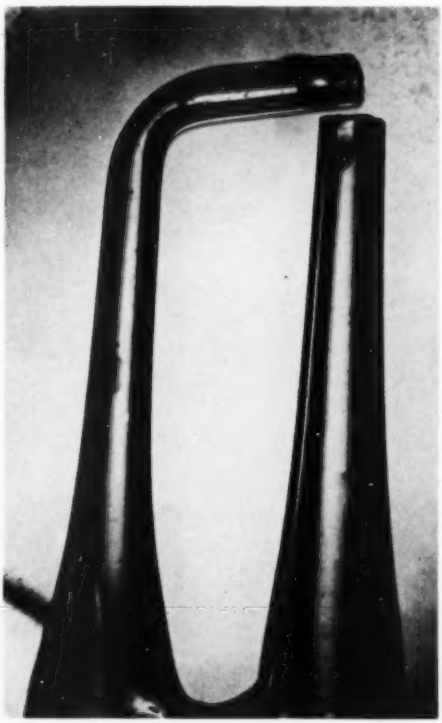


Fig. 5. DeVilbiss Nebulizer Showing Bent Capillary and Air-jet, Vertical When in Use

When a liquid is placed in the nebulizer it rises at once nearly to the top of the capillary tube by virtue of capillary action alone. Air forced through the air-jet tube then passes both around and over the capillary raising the liquid level (Bernoulli effect) slightly above the top where it is blown away and atomized. Experience dictates that the optimum position for the air-jet is almost completely *below* the top edge of the capillary but that it is directed slightly *upward*. (See Fig. 3.)

In a DeVilbiss nebulizer both capillary and air-jet are vertical except the tip of the capillary which is bent over at a right angle so as to intercept the air-stream from the jet. (Fig. 5.) The atomized spray is then carried upward nearly 3 cm. where the nebulizer makes a right-angle turn to the outlet. Some of the large drops fall out of the stream on its way up, and some impinge upon the walls at the turn.

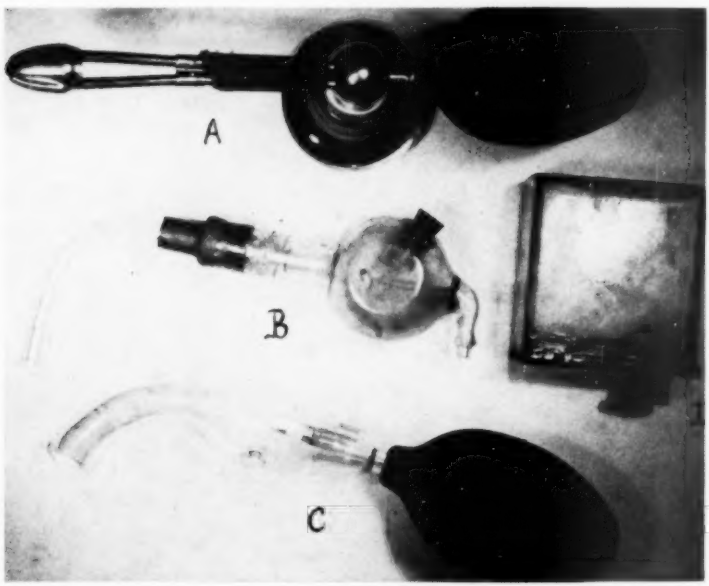
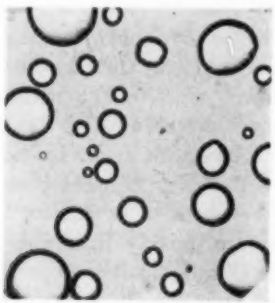


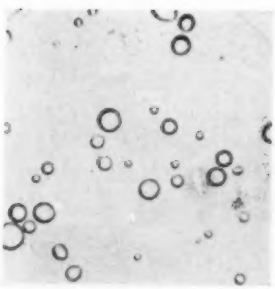
Fig. 6. Devices Used (Top View)
A. DeVilbiss Atomizer #127
B. Vaponefrin Nebulizer
C. DeVilbiss Nebulizer #40
D. Glass Cell (On Side)

This would seem to be a less efficient method of eliminating the large drops than by means of a baffle. Proof that this is so will be given later. (Fig. 9.) The atomizer and the two nebulizers are shown in Figure 6.

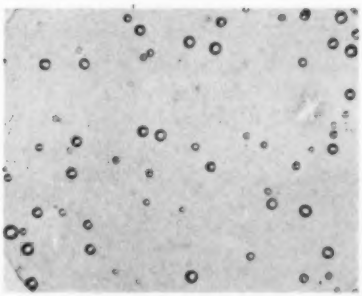
The size and distribution of droplets in a nebulized mist depend not only upon the type of nebulizer used but also upon the properties of the liquid and the pressure of the gas stream that produces them.



A. DeVilbiss Atomizer



B. DeVilbiss Nebulizer



C. Vaponefrin Nebulizer

Fig. 7. Water Droplets from Different Appliances All at the Same Air Pressure. Magnification 53X
Droplet Size is Dependent upon Appliance

The significant properties of the liquid are surface tension, density and viscosity. Their magnitudes for diethylene glycol and machine oil compared with those of water are given in Table I.

TABLE I

Liquid	T	ϱ	η
d-glycol	.5	1.2	30
oil	.3	.9	300

High viscosity should slow up the rate of delivery and reduce the diameter of a liquid filament thus tending to create small droplets; but these effects are offset by sluggishness of movement of the liquid at the point where drops begin to form which tends to retard break-up of the jet. The result is an approximate balance so that particle size has been found to be nearly independent of viscosity. The predominant factor seems to be surface tension, which bites off a filament of water more quickly than one of either of the other liquids used and hence creates smaller drops. From the meager data available it was found that droplet size roughly varied inversely as surface tension.

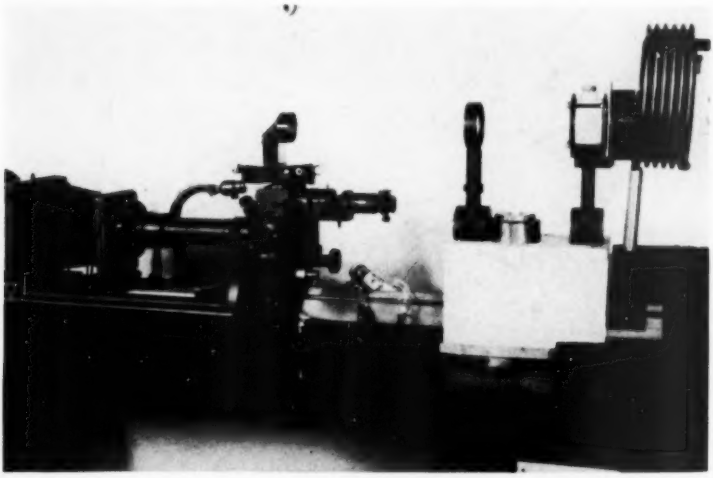


Fig. 8. Zeiss Neophot with Tungsten Arc Light Source

The velocity of the gas in the air-jet increases with the pressure (above atmospheric) up to the point where the stream becomes turbulent. Below this point higher pressure should generate smaller droplets, since the faster stream makes finer liquid filaments. However, turbulence sets in so soon that all normal operation of atomizers and nebulizers takes place at a pressure (25 cm. of mercury) several times this critical value (4-5 cm. of mercury); hence the average size of drops is independent of the gas pressure in the jet. It is also independent of the nature of the gas (oxygen, nitrogen, air).

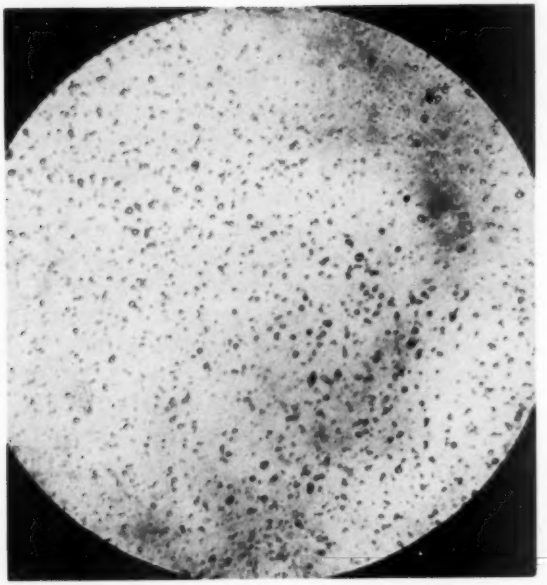
Both Vaponefrin and DeVilbiss nebulizers produced small droplets of about the same size, but the size of the large drops depends upon the appliance used to create them, as is seen in Figure 7. These samples of mist were all produced at the same pressure in the jet which was blown with oxygen from a pressure tank. All small droplets had evaporated before the slide could be photographed. Those that remain are in the medium and large size group.

A new technique * has been employed which makes possible the microphotography of a sampling of either sprays or mists in such a manner that the size distribution of droplets as photographed duplicates very nearly the distribution in the actual spray or mist.

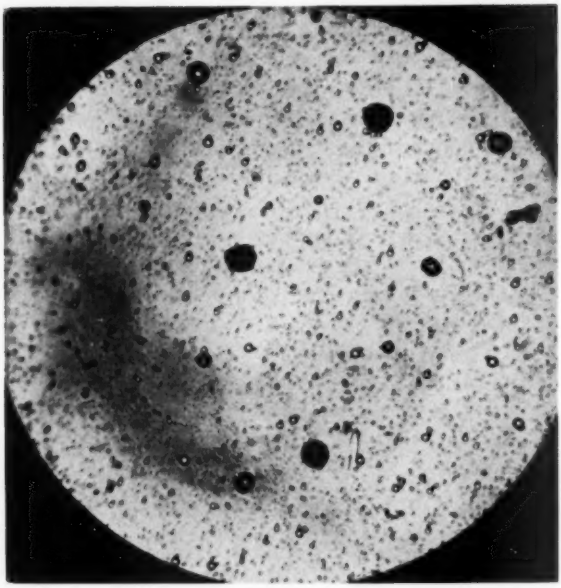
Droplets of water or glycol are allowed to settle upon the surface of a thin layer of oil which they penetrate, since they have greater density, but to the *under side of which they cling* supported partly by the displaced oil and partly by surface tension. Drops above a critical size, which is rather large, are too heavy to be sustained by the weak surface tension of the oil ($T = 32$ dynes/cm) and therefore fall to the bottom out of the plane occupied by the small droplets. If the layer of oil is not over 1 mm. thick, such large drops may be detected by the fuzzy images which they produce on a photograph of the small droplets when the camera is focussed on the plane of the latter.

The following procedure was adopted:—(a) A small glass cell was constructed (2 x 2 x 1 in.) with clear glass at top and bottom, and a hole in one end through which spray or mist could be introduced. The hole was then stoppered. (b) The bottom of the cell was covered to a depth of not over 1 mm. with oil. Machine oil or liquid petrolatum (Nujol) proved satisfactory, but castor oil was unsatis-

* A modification of that described in a communication from Prof. Louis G. Dunn, Director of the Jet Propulsion Laboratory, California Institute of Technology. The drops photographed there were much larger than those studied here.



A. Vaponefrin Nebulizer



B. DeVilbiss Nebulizer

Fig. 9. Mists Photographed with the New Technique. Magnification 78X.

factory probably because these droplets were too light to penetrate the surface of such a highly viscous liquid. (c) Microphotographs were taken with a Zeiss neophot using light from a tungsten arc through a water jacket reflected down through the cell by a right-angle prism on its top (Fig. 8.) Thus the photographs were made through the bottom of the cell and the layer of oil covering it.

This technique insures that the droplets are all spherical when photographed, and also that they do not evaporate, since they are enclosed in oil. Absence of evaporation was confirmed by the observation that in two hours the pattern of droplets as seen in the observing microscope did not change.

In Figure 9 is shown a microphotograph of mist from each of the nebulizers taken in the manner described above. The small droplets from each nebulizer are of nearly the same size (1-2μ). Droplets of medium size have not been completely eliminated by the DeVilbiss nebulizer, but there are no large drops like those produced by the atomizer. Either nebulizer produces a mist which should be suitable for use in the treatment of diseases of the respiratory tract. Microphotographs such as these have been duplicated many times leaving no doubt that they represent the true physical conditions of the respective aerosols.

During the past few years the spray technique has been adopted in many industries,—painting, oil burners, Diesel motors, spreading of insecticides, etc. An industry may require very different characteristics of particle size and distribution from those imposed by inhalation therapy, yet knowledge of what those characteristics are is basic. By the use of a suitable oil (for large drops castor oil) in the glass cell (Fig. 6) drops of any size can be photographed. As an example, Figure 10 shows the characteristic spray from a simply constructed "Flit" gun with a range of particle size of 10-50μ. The absence of all particles with a diameter less than 10μ may be noted.

Summary

An aerosol suitable for use in inhalation therapy, consisting of droplets 1-2μ in diameter, can be produced by either of two types of nebulizer. That produced by the Vaponefrin nebulizer is of nearly uniform particle size. The size is independent of the pressure of atomization above 5 cm. of mercury.

The particle size is independent of the viscosity of the liquid over a wide range, but depends upon its surface tension. The higher the surface tension the smaller are the droplets.

A new technique has been used in the microphotography of a sampling from a mist. The droplets are caught on the under surface of a layer of oil, hence there is neither distortion of shape nor evaporation. The character of the mist is apparent from a glance at such a microphotograph.

By the use of a suitable oil the technique described may be adapted to the photography of droplets in other size ranges such as those used in various industrial applications.

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THE SEX HORMONES

A Review

THE sex hormones are of particular interest to pharmacists and laymen alike. Their actions on the body are of tremendous importance since they are involved in such fundamental matters as reproduction, the sex drive, body shape and contour, and even one's basic motivations. Much has been written about these substances in the public press. Unfortunately, not all of the popular articles are scientifically correct. In this article we shall try to present important facts concerning sex hormones so that the pharmacist may be prepared to answer questions concerning them and also dispense them on prescription with professional skill.

Sex Physiology in the Female

It is quite essential that one understand the vital role which the sex hormones play in normal sex physiology. With this knowledge the action of sex hormones as medicinal substances can be more readily understood.

At the time of puberty in the young girl the pituitary becomes quite active and pituitary gonadotrophins are secreted in relatively large amounts into the circulating blood. In the female the gonads or sex glands are the ovaries. Under the stimulus of pituitary gonadotrophins the ovaries tend to mature and eventually the effect of gonadotrophin I (FSH or follicle stimulating hormone) causes an ovarian follicle to ripen. At the same time that this follicle is ripening a new hormone is produced in the follicle. This new hormone is known both as follicular hormone and as estrogen. (The reason for this latter name will be explained later.) This hormone, estrogen, has some very profound effects. In the young it causes the growth of the uterus and vagina and produces the body contour which is typically feminine. These are described as secondary sex characteristics. Once the girl matures and menstruation begins estrogen is an essential in causing this cycle. The events taking place in the menstrual cycle are as follows: Under the influence of FSH from the anterior pituitary the ovarian follicle develops and secretes estrogen into the circulating blood. This causes a proliferation of the uterine

endometrium. After about 14 days the ovum is ripe and it is released, passing slowly down through the Fallopian tube and into the uterus. With the release of the ovum the second gonadotrophin from the anterior pituitary, LH or luteinizing hormone, causes the formation of corpus luteum in the follicle from which the ovum was released. A third substance secreted by the anterior pituitary, luteotrophin, stimulates the corpus luteum to secrete estrogen and also a second female sex hormone called progestin. Under the combined influence of estrogen and progestin the uterine endometrium now develops secretory glands and the endometrium is said to be in the secretory phase. This takes place in order to care for the ovum in the event it has been fertilized by a spermatozoon from a male. If such a fertilized ovum is present it attaches itself to the endometrium and is nourished by it. Placental tissue develops together with the fetus which it nourishes until the time of birth.

The continued secretion of estrogen and progestin by the corpus luteum is absolutely essential during the early weeks of pregnancy. Animal experiments have proven that pregnancy is abruptly terminated if the ovaries (with their corpus luteum) are removed. The need for estrogen and progestin during pregnancy is to maintain the placenta which in turn nourishes the fetus. The continued activity of the corpus luteum during early pregnancy is maintained by the stimulating action of chorionic gonadotrophin, a hormone secreted during early pregnancy by a certain portion of the placenta.

In the human pregnant female corpus luteum activity ceases at about the third month. At this time the placenta takes over the manufacture of estrogen and progestin which it needs. This transitional period is at times accompanied by some chance of a miscarriage.

If the female is not fertilized during the fertile period the ovum is discarded, and at about day 28 the corpus luteum activity ceases. This causes an abrupt drop in the estrogen and progestin level of the circulating blood. This in turn brings the secretory phase of the uterine endometrium to an end. The superficial tissue sloughs off with bleeding causing menstruation to take place. The periodicity of menstruation is explained by the fact that estrogen restrains pituitary activity. When the level of estrogen drops at the beginning of menstruation, pituitary activity increases causing a new follicle to begin to ripen and the process repeats itself. Eventually the ovaries no longer respond properly to pituitary stimulation and the menopause takes place. The menstrual periods are irregular and scanty

or profuse. Finally, they cease altogether. The unpleasant side effects of the menopause are caused largely by the failure of the estrogen supply which permits excessive pituitary activity without the restraining effect of estrogen. This leads often to vasomotor and emotional disturbances.

Sex Physiology in the Male

Male physiology is much more simple than that of the female since no menstrual cycle is involved. The pituitary gonadotrophins in the male are identical with those in the female. Gonadotrophin I causes the growth and maturation of spermatozoa in the seminiferous tubules. Gonadotrophin II stimulates the interstitial cells of the testes to produce and secrete the male sex hormone called androgen. It is androgen which causes the penis and prostate to grow, the voice to deepen and the male body contour and hair distribution. In the male, just as in the female, it is the increased pituitary activity at puberty which stimulates the gonads leading to rapid changes in the individual. In old males there is no period exactly comparable to the menopause in females. Diminished gonadal activity with advancing age may cause emotional disturbances, notably depression and many physicians attribute this to a lowered androgen level.

The Nature of the Sex Hormones

All of the natural sex hormones both male and female are steroids. As steroids they are derivatives of the perhydro-cyclopentano-phenanthrene nucleus. Only slight differences in structure are present when one compares the male and female sex hormones and yet they are almost opposite in their effects.

Estrogens

The term estrogen means "estrus producing". It was coined after it was found that these substances when injected into test animals caused a cornification of the vaginal mucosa characteristic of estrus or "heat". The natural estrogen of the female is believed to be alpha-estradiol. Other closely related compounds such as estrone and estriol are probably decomposition products, although they still have some activity. The urine of pregnant mares is rich in natural estrogens. These substances, after extraction, constitute the product "estrogenic substance" which is effective when injected. When

conjugated as a sulfate they are effective orally. Such products are known as conjugated estrogens. It is a rather unusual fact that the urine of stallions is even a richer source of natural estrogens than is the urine of pregnant mares. The reason for this anomaly is not clear.

Both alpha-estradiol and estrone are made synthetically and these are used in large quantities as estrogens.

Alpha-estradiol is active both by mouth and by injection. It is usually given orally or sublingually in the free form and by injection in oil solution as the benzoate or the diproprionate. The benzoate is longer acting than the free form and the diproprionate even longer in its action.

Estradiol is also absorbed when applied to the skin in a suitable vehicle by inunction. The so-called hormone skin creams contain small amounts of estrogens. These are claimed to produce a firmness to the skin largely by reason of a local effect.

Ethinyl estradiol is the most potent estrogen when given orally. It contains the ethinyl group — C $\equiv$ CH attached on C atom #17.

In addition to the estrogens which are steroids there are a number of synthetic non-steroids having a powerful estrogenic effect. These include: Diethylstilbestrol, Hexestrol, Benzestrol, Dienestrol, Mestibol and Meprane. All of these non-steroid estrogens are related chemically to diethylstilbestrol and all are quite active by the oral route as well as by injection.

The Progestins

The second type of female sex hormone consists of the progestins. These are sometimes called the luteoids as contrasted with the estrogens which are called the folliculoids. The progestins are also steroids. It is believed that the natural female progestin is the substance progesterone. Progesterone is made synthetically and it is widely used. Progesterone is administered by intramuscular injection in oil solution and also sublingually or in the form of buccal tablets. The sublingual or buccal administration of the steroid hormones is growing in popularity since this route permits the hormone to enter the general circulation without first passing through the stomach and then the liver via the portal circulation. The stomach alters the molecule followed by the effect of the liver which inactivates the sex hormones progressively by forming conjugates which are then excreted by the kidneys.

The substance ethisterone is a progestin of great importance. It is known also as anhydrohydroxyprogesterone. This steroid has an ethinyl group on C atom #17 which permits the molecule to escape gastric degradation and be absorbed from the intestine in active form. Ethisterone is also more slowly conjugated by the liver.

The Androgens

There is only one male sex hormone rather than two as in the case of the female. The natural male hormone is the steroid, testosterone. Testosterone is very closely related chemically to progesterone, the former having an — OH group attached to C atom #17 while progesterone has the short chain — CO — CH_3 on C atom #17. Testosterone is made synthetically in large quantities. It is used in the form of pellets for tissue implantation. This permits the slow release of the hormone over a period of weeks and more closely simulates the release from the testes in normal males. A more modern form of testosterone is a suspension of "micropellets" or small crystals. This suspension is injected with the regular syringe. It, too, provides a depot from which the drug is gradually released. Another depot form is Testosterone cyclopentylpropionate which is given in oil solution by intramuscular injection. Testosterone as the propionate is used in oil solution by intramuscular injection and in buccal tablets. Methyl testosterone differs from testosterone only in the presence of a methyl group on C atom #17. It is effective when given orally and tablets of it are widely prescribed. Methyl testosterone also is employed in sublingual and buccal tablets and this dosage form is quite popular with physicians.

Clinical Uses of Sex Hormones

There are many indications for the use of sex hormones. These compounds are very potent substances. Their use without proper medical supervision is dangerous and it should be discouraged.

One of the most important uses of the estrogens is to control the vasomotor disturbances at the time of the menopause. When ovarian activity ceases the estrogen level of the blood drops and the anterior pituitary is no longer held in check. The symptoms of the menopause are caused in part by excess anterior pituitary function and in part by psychic factors. Estrogens given in proper dosage check the excess pituitary function and the typical hot flushes are brought under con-

trol. It is interesting to note that androgens such as testosterone may be used with similar results since these, too, depress pituitary function. Combinations of androgen and estrogen are today considered ideal in controlling menopausal symptoms. Estrogen alone, while effective, tends to cause proliferation of the uterine endometrium. This is considered dangerous in a patient with a family history suggesting cancer. Androgen alone tends to cause masculinization of the patient. In proper ratio a combination of the two avoids both of these undesirable side effects. A number of such combinations are now available.

Senile vaginitis responds favorably to estrogen therapy. Estrogens cause the vaginal mucosa to return to the more resistant type characteristic of mature females. Vaginitis in young female children is often helped by the administration of estrogens. Here, too, the vaginal mucosa is altered in such a way that the tissue becomes more resistant. Prior to the days of antibiotics, gonorrheal vaginitis in young girls was exceedingly difficult to cure unless specific therapy was accompanied by the use of estrogens. In the treatment of vaginitis the estrogens may be used in various dosage forms including vaginal suppositories.

Estrogens have been found to suppress the growth of prostatic cancer in males as well as its metastases. The cancer is not cured but life-expectancy may be increased up to 5 years. In post-menopausal women estrogens seem to exert a favorable effect in cancer of the breast. Estrogens must not be used for this condition in pre-menopausal women since they tend to stimulate rather than retard the cancer growth. In pre-menopausal women with cancer of the breast the androgens are employed with or without radiation of the ovaries. Significant increases in life-expectancy have been reported in such patients but side-effects such as hirsutism (hairiness) and increased libido are quite common.

Estrogens and androgens both suppress lactation and are often used for this purpose when so indicated. Here again they act by suppressing pituitary function, decreasing its output of lactogenic factor (luteotrophin).

Estrogens, in recent years, have been found very useful in preventing orchitis as a complication of mumps in mature males. If given early in the course of the disease no damage to the testes results from the infection.

Estrogens and progestins are employed with some success in treating dysmenorrhea. Progestins which tend to have a quieting

effect on the uterus are more often successful. Each patient should be studied individually and the best regimen of treatment developed for her case.

The use of estrogens and progestins in amenorrhea will definitely establish menstruation in any woman who has an intact uterus. This has been demonstrated experimentally even in senile post-menopausal women. Several regimens have been recommended. One attempts to duplicate the normal hormonal control by administering estrogen for about 2 weeks to initiate the proliferative phase of the uterine endometrium followed by the use of estrogen and progestin to cause the secretory stage. Therapy is then abruptly stopped and menstruation results. Such menstruation, although normal in appearance, is artifically produced. After several such induced periods, therapy is discontinued in an effort to have menstruation take place by the normal pituitary-ovarian cycle. Some physicians prefer the use of gonadotrophins to induce gonadal activity feeling that stimulation therapy is superior to substitution therapy providing the gonads can be stimulated.

Combinations of estrogen and progestin are available for a short term induction of menstruation. Therapy for 2 to 3 days is followed in 3 to 5 days by uterine bleeding. Such therapy does not induce abortion if the patient is pregnant since in pregnancy the uterus is very tolerant to estrogen and progestin. Actually, in normal pregnant women the blood levels of estrogen and progestin are quite high since these hormones are essential for continued pregnancy.

Estrogens have been used to correct frigidity in females but in most cases this condition is of psychic origin and not organic. Estrogens are also used by inunction in fatty vehicles to promote a growth of the breast in hypomastia.

Estrogens in skin creams are claimed to improve skin tone and cause it to assume a more youthful appearance. These claims are disputed by some authorities.

The administration of estrogens in adequate doses to males results in a "chemical castration". This is sometimes done in sex criminals and it is used in the poultry industry to caponize male chicks.

The principle use of progestins such as progesterone and ethisterone is in the control of threatened abortion. Conception itself is dependent upon corpus luteum activity and its release of progestin since the changes in the uterine mucosa essential for fixation and

nourishment of the fertilized ovum depend upon the corpus luteum. Many cases of habitual abortion can be traced to insufficient corpus luteum activity and the prophylactic use of progestins permits many of these individuals to maintain their pregnancy to full term. Some physicians prefer to use combined estrogen-progestin therapy in threatened or habitual abortion basing their judgment on the fact that the corpus luteum actually releases both types of hormones in the normal person.

Estrogen therapy in place of progestins is also claimed to produce just as satisfactory a result in threatened abortion according to recent reports.

The use of progestins in dysmenorrhea and pre-menstrual tension is based upon their inhibitory effect upon uterine motility. The effect of progestins in suppressing menstrual flow has also led to their use in menorrhagia and functional uterine bleeding. Androgens have also been used similarly.

The use of androgens in females for certain purposes has already been discussed. In males, the principal use of androgens is in relieving the depression commonly observed in older males and often described as the "male climacteric". Great benefit often results with a renewed sense of well-being and initiative. Whenever androgens are used in elderly males it is important not to give a dose of such size that the stimulation produced causes the patient to exceed his cardiovascular reserve. If this is done a heart attack or a stroke may be precipitated. Androgens have also been found to reduce the frequency and severity of anginal attacks.

Androgens are helpful in some cases of impotence but not all. In cases which are caused specifically by a testicular deficiency androgens may be indicated.

In eunuchism and hypogonadism androgens as substitution therapy promote the development of secondary sex characteristics and increases the muscular strength and tone of the body.

In cryptorchidism (undescended testes) stimulation therapy with gonadotrophins is preferred, although this may in some cases be supplemented with androgen therapy.

Androgens have a distinct anabolic effect (body building) and this has led to their use in the treatment of premature infants and underdeveloped children. Nitrogen retention and weight gain usually results. Just recently a compound, methandriol, has been announced which has the anabolic effect of the androgens without their marked

androgenic effects. Methandriol is closely related to testosterone differing only in having a Δ_5 double bond instead of Δ_4 and an alcohol group at C #3 instead of a ketone.

The required dose of any given sex hormone varies greatly with the product, its route of administration, the condition being treated and the patients response to therapy. Space does not permit the precise dosage schedule recommended for each of the above clinical uses.

Products

The number of products in the sex hormone field is unbelievably large. Not only are there many products containing single hormones but many combinations are marketed. In many instances combinations are warranted such as the estrogen-androgen mixture used in the menopause. Other entirely rational combinations such as estrogen and phenobarbital are quite common.

SELECTED ABSTRACTS

Vitamin K in Hypoprothrombinaemia. Douglas, A. S. and Brown, A. *Brit. Med. J.* No. 4755:412 (1952). Because of the danger of hemorrhage from the administration of dicoumarol or Tromexan in the treatment of thromboembolic states a reliable antidote would be of great value. Vitamin K and related compounds have proven to be capable of reversing the hypoprothrombinemia produced by the above anticoagulants. In this study the authors have sought to evaluate some of the vitamin K preparations that are available.

Either dicoumarol or Tromexan was administered in therapeutic doses to patients in whom there was no obvious potential source of hemorrhage or evidence of hepatic, alimentary, or renal dysfunction. A number of vitamin K preparations were tested as follows: vitamin K_1 (2-methyl-3-phytyl-1:4-naphthoquinone) intravenously in single doses of 200 to 340 mg; menadione (2-methyl-1:4-naphthoquinone) intramuscularly in doses of 15 to 30 mg. over 2 to 3 days; Prokayvit (2-methyl-1:4-naphthohydroquinone diacetate) orally in a dose of 90 mg. in 3 days; Kapilon (2-methyl-1:4-naphthohydroquinone carboxymethoxine) intramuscularly in a dose of 60 mg. in 3 days; Synkavit (2-methyl-1:4-naphthohydroquinone diphosphate) intravenously in a dose of 300 to 1600 mg. in 3 to 4 days; and water soluble K analogues (dipotassium 2-methyl-1:4-naphthylene bisulfate) intravenously in a single 200 mg. dose.

Vitamin K_1 was the only substance found to be consistently effective as an antidote and in blocking the action of therapeutic doses of both dicoumarol and Tromexan. Kapilon showed slight but significant modication of the prothrombin time when used against dicoumarol but in no case did the prothrombin time return to normal within 3 days. Some of the other preparations showed slight but not significant antidotal effects. When vitamin K_1 was given at the same time as the anticoagulant the effect on the prothrombin time was almost completely inhibited. When the vitamin was given after hypoprothrombinemia had been induced the prothrombin levels were restored to normal within 24 hours, and safe values were obtained within 6 to 9 hours.

A New Local Treatment for Burns. Spangler, P. E. *U. S. A. F. Med. J. 3:*105 (1952). A new method and application for the treatment of burns was employed by the author in 22 unselected cases. The principle of the method, however, is not new, namely, that of an effective occlusive dressing which keeps contaminants out and vital fluids and tissue components in, where they can aid the healing process.

The method employs the application of about 1/16 of an inch of a sterile gel, composed of partially hydrolyzed casein, sodium lactate, and sodium lauryl sulfate, to the burned area without debridement other than the evacuation of large blisters and the removal of loose necrotic skin. Then a four-ply, course-meshed gauze, impregnated with zinc acetate is applied lengthwise and pressed down so that the gel penetrates the meshes of the gauze. The dressing is then secured with an elastic bandage. The gel soon sets and covers the burn area with an adherent, impervious, protective membrane.

The author concluded that this method provides several advantages over any other local treatment for burns. The dressing can be easily and quickly applied. Amelioration of pain and distress is marked and rapid after application of the dressing. The incidence of infection in the burned areas is greatly reduced. In fact, no infections occurred when the dressing was applied promptly after injury. There is no loss of serum from the burned areas. First and second degree burns can be healed in from 5 to 12 days and areas of third degree burns are self-debrided and ready for split grafts sooner (from 12 to 14 days) than with other methods. Healing is accompanied with a minimum of scarring. Finally, the patient is able to attend to many of his personal needs because of the flexibility of the dressing, and thus nursing care is reduced.

Treatment of Pulmonary Tuberculosis With Combined Streptomycin-Tuberculin. Jacobs, E. C. and Vivas, J. R. *U. S. A. F. Med. J. 3:*115 (1952). The inability of streptomycin to clear many tubercular lesions is believed to be due to the avascularity and fibrous encapsulation of the tubercles, resulting in a failure of the antibiotic to penetrate into the lesions in sufficient concentration to produce tuberculocidal action. The addition of tuberculin to the streptomycin increases the vascularity of the tuberculous lesions and in-

creases the permeability of the involved vessels. This permits greater penetration of the antibiotic into the lesions. A greater concentration of the antibiotic in the lesions may also reduce the incidence of the development of resistance to streptomycin for, it is believed that the development of resistance has been due to the low concentrations of streptomycin within the lesions.

The authors reported the results obtained with a series of 24 unselected patients with pulmonary tuberculosis who were treated with combined streptomycin and tuberculin therapy. After an observation period of 2 to 4 years there were 19 of the patients alive, 8 were apparently cured, the disease was arrested in 8, and 3 had active tuberculosis. However, the authors stated that the abeyance of clinical symptoms, roentgenographic improvement, sputum conversion, decrease in sedimentation rate, pulse and temperature, and increase in body weight, appetite and well being were greater and more rapid than in any similar series treated with streptomycin and other agents. There were no untoward reactions and toxicity was of little significance. Relapses were uncommon and resistance to streptomycin developed in only 9 per cent of the 22 patients, out of a larger group of 100 patients also treated by this method, in whom the sputum remained unconverted. A relatively short period of hospitalization of only about 2 months was required when the combined therapy was employed. This is an added advantage for both the patient and the hospital.

The Effects of Cortisone on the Oxidation Metabolism of the Rat Adrenal. Sourkes, T. L. and Heneage, P. *Endrocrinol.* 49:601 (1951). Previously it has been demonstrated that repeated injections of large doses of cortisone acetate into rats results in atrophy of the adrenal cortex. The probable cause of the adrenal atrophy is the suppression of ACTH release from the pituitary.

Cortisone was administered to young albino rats in doses of 3 mg. per day subcutaneously for 6 days. The animals were then killed and oxidative metabolism was studied on homogenates prepared from the atrophied adrenals as well as from the adrenals of normal control rats. The adrenals of the animals treated with cortisone showed a decreased endogenous respiration as well as greatly reduced rates of oxidation of various intermediates of the Kreb's cycle. The de-

crease in these rates cannot be accounted for solely on the basis of the reduction in the amount of cortical tissue in the atrophied glands. These results were obtained by the direct measurement of oxygen uptake in Warburg vessels.

Salmonella Infections Treated With Chloramphenicol and Terramycin. Zimmerman, L. E. *U. S. A. F. Med. J. 3*:503 (1952). The treatment of salmonella fever, salmonella septicemia, and salmonella carriers has met with many difficulties. Immune serums, bacteriophage, sulfonamides, penicillin, and streptomycin have all been used with disappointing or equivocal results. The author reported on the prompt response obtained with chloramphenicol and terramycin in the treatment of 7 cases.

Chloramphenicol was administered to 4 patients with salmonella fever, in 3 of which *S. paratyphi* and in one of which *S. schottmulleri* was the causative agent, and to 1 patient with salmonella septicemia in which *S. choleraesuis* was the causative agent. Terramycin was administered to 1 patient with salmonella fever caused by *S. typhosa* and *S. paratyphi* and to 1 typhoid carrier with *S. typhosa*. Both of the antibiotics were usually administered in an initial dose of 2 Gms. followed by 0.5 Gm. every 6 hours. The total dosage given ranged from 16 to 32 Gms. of chloramphenicol and was 14 and 10 Gms., respectively, of terramycin.

The clinical result obtained in each of these cases was gratifying. The fever was eliminated in an average of 6 days in the 6 clinical infections treated. The patient who was a carrier responded with negative rectal swab cultures after therapy but it was only possible to follow this patient for one week after therapy was begun.

The author also reported that previous sensitivity studies with 22 strains of *S. paratyphi* showed that chloramphenicol and terramycin both produced lower sensitivity levels than did aureomycin. Aureomycin was not found to be effective in the two instances that it was tried clinically. The authors, therefore, concluded that chloramphenicol and terramycin appear to be quite promising in the treatment of salmonella infections and that they appear to be superior to aureomycin.

BOOK REVIEWS

Heterocyclic Compounds. Volume 2. Edited by Robert C. Elderfield, Columbia University. John Wiley and Sons, Inc., New York, 1951. vii + 571 pp. 15.5 x 23.5 cm. Price $15.00.

This volume of Heterocyclic Compounds considers the chemistry of five and six membered polycyclic compounds containing one oxygen or one sulfur atom.

The chapter headings are:

1. Benzofuran and its Derivatives
2. Isobenzofuran, Phthalan and Phthalide
3. Dibenzofuran (Diphenylene Oxide)
4. Thionaphthene
5. Dibenzothiophene
6. Coumarins
7. Isocoumarins
8. Chromones, Flavones and Isoflavones
9. Chromenols, Chromenes, and Benzopyrrylium Salts: The Anthocyanins
10. Chromanones, Flavanones, Chromanols, and Flavonols: Catechin, Brazilin and Hematoxylin
11. Chromans
12. Xanthones, Xanthenes, Xanthydrols and Xanthylium Salts
13. Fluorans, Fluoresceins, and Rhodamines
14. Thiochromans and Related Compounds

In general, the order of presentation follows the scheme, methods of preparation, and reactions of parent compounds followed by the methods of preparation and reactions of their derivatives. In a num-

ber of instances, tables are used to summarize the isolation and the chemistry of naturally occurring products. There are, also, references and a brief discussion of the pharmacology of certain compounds.

This reviewer feels that more recognition might have been given the individual authors since approximately two-thirds of the book was the work of a single author.

The book is well done, adequately documented with 2255 references, and is highly recommended.

N. RUBIN

Medicinal Chemistry, Volume I. C. M. Suter, Editor-in-chief. John Wiley and Sons, Inc., New York, 1951. vii + 473 pp. 15.5 x 24 cm. Price $10.00.

The volume, as the title indicates, is the first in a series of reviews prepared under the auspices of the Division of Medicinal Chemistry of the American Chemical Society. The topics covered in this volume are:

1. Antithyroid Compounds
2. Antispasmodics. Derivatives of Carboxylic Acids
3. Antibiotics from Plants
4. Benzoates and Substituted Benzoates as Local Anesthetics
5. Analgesics: A. Aralkylamines
6. Analgesics: B. Partial Structures Related to Morphine

In general, each topic is discussed as to general methods of synthesis, methods of testing, pharmacological data, and, where possible, correlation of structure with activity. There are extensive tables with references and, in most cases, mention is made of the date to which the literature has been covered.

The book will be useful to chemists and pharmacologists interested in synthetic medicinals.

N. RUBIN

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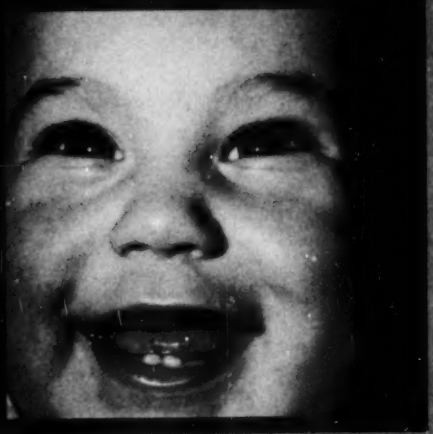

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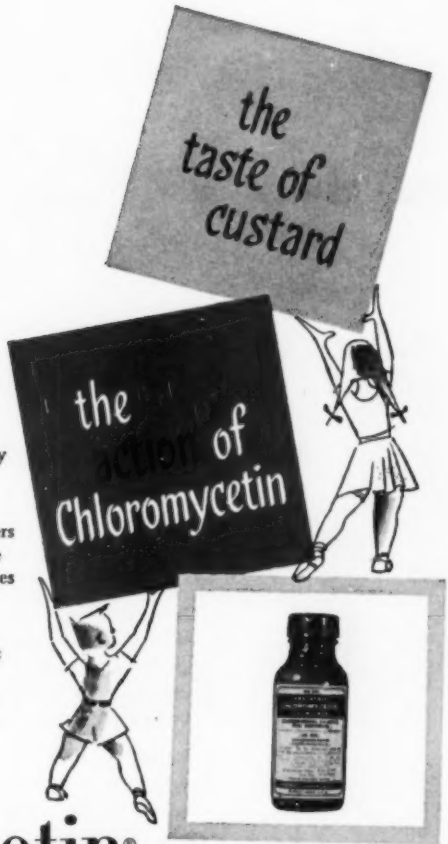

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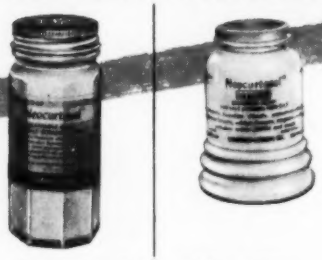

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